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ARTICLE PRINCIPAL

recouvrant en partie

la THESE présentée

en vue de l'obtention

du grade de DOCTEUR ès SCIENCES

à l'Université Pierre et Marie Curie
- Paris 6 -
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par Mr PERAYA David
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Sujet de la thèse: ETUDE CONFORMATIONNELLE THEORIQUE DES
ACIDES NUCLEIQUES, DE LEURS CONSTITUANTS ET DES SYSTEMES
MOLECULAIRES APPARENTES.

soutenue le 25 Avril 1975
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devant le Jury composé de:

Mr PULLMAN	Président
Mr DAUDEL	Examineurs
Mme SERRE	
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BBA 98018

MOLECULAR ORBITAL CALCULATIONS ON THE CONFORMATION OF NUCLEIC ACIDS AND THEIR CONSTITUENTS

XI. THE BACKBONE STRUCTURE OF (3'-5') and (2'-5')-LINKED DIRIBOSE MONOPHOSPHATES WITH DIFFERENT SUGAR PUCKERS

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Summary

The PCILO (ω' - ω) conformational energy calculations on (3'-5') and (2'-5')-linked diribose and (3'-5')-linked dideoxyribose monophosphates with different sugar puckers and different geometries of the phosphate group corresponding to the known crystal structures of $U_3 \cdot p_5 \cdot A$ and $A_2 \cdot p_5 \cdot U$ show that the disugar backbone provides stable arrangements in the right and left-handed folded conformations. The occurrence of these folded conformations depends to a large extent on the geometry used for the phosphate group and generally the following rule remains valid: the right-handed folded conformation is favored when the $O_5 \cdot PO(I)$ and $O_3 \cdot PO(II)$ valence angles are greater than their symmetrical value while the left-handed folded conformation is favored when these valence angles are smaller than their symmetrical value. In a few cases associated with specific combinations of the linkage and the sugar puckers the preferred folded conformations are changed. As far as the effect of linkage is concerned, the greatest probability of occurrence of the right-handed folded conformation is found generally for (3'-5')-linked dimers and the greatest probability of occurrence of the left-handed folded conformation for (3'-5')-linked deoxyribose and (2'-5')-linked ribose dimers.

Introduction

In the previous papers of this series devoted to studies by the quantum-mechanical PCILO method of the conformation of nucleic acids and their constituents, the interest was centered on the study of the conformational properties of the nucleoside and nucleotide units [1–10]. An attempt was also undertaken to study the conformation about the disugar phosphate backbone



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[11]. This was done for the case of (3'-5')-linked diribose phosphate with a C(3')-endo conformation of the sugars.

The aim of the present study is the comparison of conformations about the two P—O ester bonds in (3'-5') and (2'-5')-linked diribose monophosphates, with a concomitant investigation of the effect of varying the sugar pucker.

In one of our preceding articles [12] of this series we have established a correlation between the geometry of the phosphate group and the preferred conformations about the two ester P—O bonds in dimethyl phosphate. In particular, it was shown that the g^-g^- conformation is favored when the $O_5 \cdot PO(I)$ and $O_3 \cdot PO(II)$ valence angles (see Procedure and Fig. 1) are greater than would have been their symmetrical value and that the g^+g^+ conformation is favored when these same valence angles are smaller than their symmetrical value. A confirmation of this rule was accomplished by analyzing the geometry of the phosphate group in the crystal structures of diethyl phosphates. It was also shown that this rule is valid for all known X-ray crystal structures of dinucleoside monophosphates.

In addition to the effect of linkage and sugar puckers on the torsion of the P—O ester bonds, we try to investigate to what an extent the rule stated above remains valid in model molecules of disugar monophosphates, following a variation in the linkage (3'-5' or 2'-5') and sugar pucker.

The subject is under active investigation by a variety of techniques. Experimental studies in solution have been performed extensively on dinucleoside monophosphates, including ribodimers with different phosphodiester linkages [3'-5', 2'-5' and 5'-5') and different base pairs [13-24], as well as deoxyribodimers [16,23,25,26]. A limited number of X-ray crystal structures of dinucleoside monophosphates have also been established: they include three molecules with a (3'-5') linkage, namely $U_3 \cdot p_5 \cdot A$ [27,28], $A_3 \cdot p_5 \cdot U$ [29] and $G_3 \cdot p_5 \cdot C$ [30] and one molecule with a (2'-5') linkage namely $A_2 \cdot p_5 \cdot U$ [31]. Very recently the X-ray crystal structure of a trinucleoside diphosphate, $A_3 \cdot p_5 \cdot A_3 \cdot p_5 \cdot A$ has been established (ref. 32 and Suck et al. private communication).

In spite of these investigations no clear-cut conclusions are as yet available about the differences in the backbone conformations in the (3'-5') and (2'-5')-linked dimers or on the effect of the different sugar puckers. In particular, the experimental studies involving always the presence of purine and/or pyrimidine bases, it remains an open problem to determine to what an extent are the observed conformational properties of dinucleoside phosphates due to the intrinsic tendency of the sugar-phosphate backbone and to what an extent are they influenced by the presence of the bases. The determination of the conformational preferences of diribose monophosphates carried out in this paper represents an attempt to answer this question. The extension of the study to dideoxyribose analogues is intended to contribute to the solution of an other ambiguous problem, namely the role of the 2'-hydroxyl group of the sugar, a large division of opinion existing about its hydrogen bonding [24] or steric influences [16,21].

Procedure

The method employed in this investigation is the PCILO (Perturbative Configuration Interaction using Localized Orbitals) method developed recently in our laboratory [33–36].

The structure of a (3'-5')-linked diribose monophosphate is represented in Fig. 1, which contains also the indications of the notations used for the torsion angles of the backbone and of the hydroxy groups of the sugar units. The same notations are kept in the study of the (2'-5')-linked diribose monophosphates with the appropriate change in the position of the linkage, and in deoxyribose dimers in which the 2'-OH groups have been substituted by hydrogens. The bond lengths and angles adopted as input data in the calculations are taken from the crystal structure of $A_2 \cdot p_s \cdot U$ [31]. They have been preferred over those related to the crystal structure of $U_3 \cdot p_s \cdot A$ [27,28], the main reason for this being that the former presents both types of sugar pucker (C(3')-endo and C(2')-endo) instead of only one type in the latter (C(3')-endo); it was thus more convenient to use the data on these two types of sugar pucker in all the performed combinations. In the least-squares planes description of Sundaralingam [37] the two sugar pucker existing in the crystal structure of $A_2 \cdot p_s \cdot U$ belong to the 2T_1 and 3T_2 twisted conformations [38].

The definitions and conventions utilized throughout this paper are those of Sundaralingam [39] and are given also in our previous papers in this series [11,12]. One supplementary precision must, however, be given for the rotational angle Φ' ; in (3'-5')-linked dimers the 0° torsion angle is defined by the *cis* planar position of O_3 -P bond with respect to C(3')-C(4') bond and in (2'-5')-

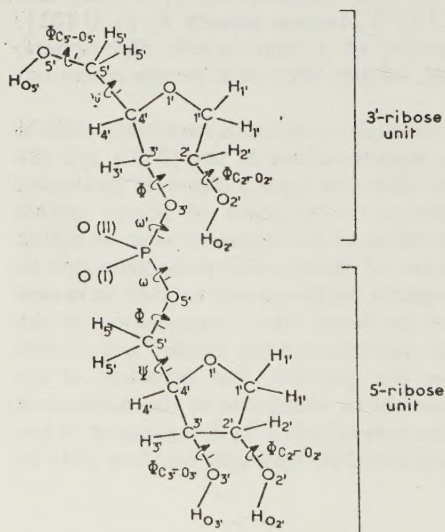


Fig. 1. Torsion angles and notations of disugar monophosphate.

linked dimers by the *cis* planar position of O₂'-P bond with respect to C(2')-C(3') bond. The torsion angles related to the sugar OH groups are defined as follow:

$$\Phi_{C(5')-O(5')} = C(4')-C(5')-O(5')-H(O5')$$

$$\Phi_{C(3')-O(3')} = C(2')-C(3')-O(3')-H(O3')$$

$$\Phi_{C(2')-O(2')} = C(3')-C(2')-O(2')-H(O2')$$

The combination of the sugar puckers in a dimer are designated within parenthesis, the first pucker referring to the 3'-sugar unit and the second one to the 5'-sugar unit (e.g. (C(2')-endo, C(3')-endo) indicates that the 3'-ribosyl unit has the C(2')-endo sugar pucker and the 5'-ribosyl unit the C(3')-endo sugar pucker).

Our study has been centered essentially on the construction of the (ω' - ω) conformational energy maps corresponding to rotations about the two P-O ester bonds. The remaining torsion angles are considered fixed in preselected values corresponding to the most frequently observed values in crystal structures of nucleic acids [38,39]. These preselected values are; $\psi = 60^\circ$, $\Phi = 180^\circ$, $\Phi' = 200^\circ$ for (3'-5')-linked dimers and $\Psi = 60^\circ$, $\Phi = 180^\circ$, $\Phi' = 240^\circ$ for (2'-5')-linked dimers. For the rotation of the hydroxy groups the values adopted are; in the 5' unit, $\Phi_{C(2')-O(2')} = 60^\circ$, $\Phi_{C(3')-O(3')} = 180^\circ$; in the 3' unit, $\Phi_{C(5')-O(5')} = 180^\circ$, $\Phi_{C(2')-O(2')} = 300^\circ$ for (3'-5')-linked dimers, $\Phi_{C(3')-O(3')} = 180^\circ$ for (2'-5')-linked dimers.

Two different phosphate group geometries have been considered concomitantly in the evaluation of the (ω' - ω) conformational energy maps. One of them favors the g^-g^- region in dimethyl phosphate [12] and is taken from the crystal structure of ApU [31]. The second favors the g^+g^+ region in dimethyl phosphate [12] and is taken from the crystal structure of UpA2 [28]. The consideration of two different phosphate geometries, one favoring the g^-g^- and the other the g^+g^+ regions in the discussion of the (ω' - ω) conformational energy maps is of prime importance in order to have both regions equally favored in so far as the inherent properties of the phosphate group are considered. The role of the nature of the linkage and of the type of the sugar on the stability of the g^-g^- and g^+g^+ regions can then be easily discussed.

The region of the right-handed folded or the g^-g^- conformation is defined by the following nine conformations; (ω', ω) = (240°, 240°), (270°, 240°), (300°, 240°), (240°, 270°); (270°, 270°), (300°, 270°), (240°, 300°), (270°, 300°), (300°, 300°); the region of the left-handed folded or g^+g^+ conformation is defined by the following nine conformations; (ω', ω) = (60°, 60°), (90°, 60°), (120°, 60°), (60°, 90°), (90°, 90°), (120°, 90°), (60°, 120°), (90°, 120°), (120°, 120°).

The methodology for the calculation of probabilities of occurrence of these regions [40] has been indicated in one of our previous articles [12].

Results

(ω' - ω) Conformational energy maps

The (ω' - ω) conformational energy maps of (3'-5') and (2'-5')-linked

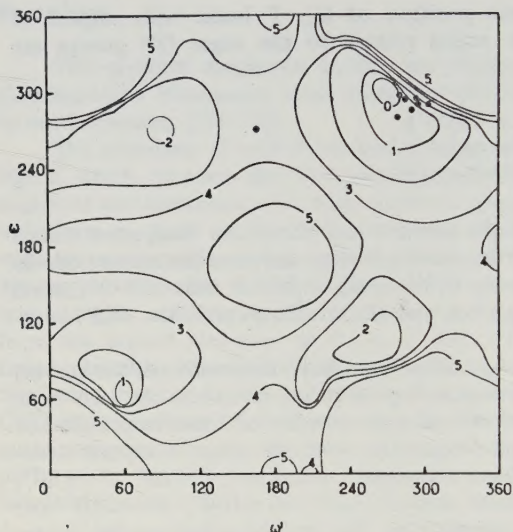


Fig. 2. $(\omega'-\omega)$ conformational energy map of (3'-5')-linked C(3')-endo, C(3')-endo diribose monophosphate with the phosphate group geometry taken from ApU [31] which favors the right-handed folded conformation. Isoenergy curves (kcal/mole) with respect to the global minimum taken as energy zero. (●) X-ray crystal structure data.

diribose monophosphates, with for each of them the two phosphate geometries favoring, respectively, the g^-g^- and g^+g^+ regions, have been evaluated for the four possible combinations of the two fundamental sugar puckers, C(3')-endo and C(2')-endo. In addition, we have also evaluated the $(\omega'-\omega)$ conformational energy maps of (3'-5')-linked dideoxyribose monophosphates having the same different phosphate group geometries cited above. This however, was done only for the two following sugar pucker combinations; C(3')-endo, C(3')-endo and C(2')-endo, C(2')-endo. Because of the large number of conformational maps built we shall only present the most representative ones.

(3'-5')-Linked ribose dimers. We present in Fig. 2 the $(\omega'-\omega)$ conformational energy map corresponding to the (3'-5')-linked C(3')-endo, C(3')-endo diribose monophosphate with the phosphate group geometry favoring the g^-g^- region. The global minimum is situated at $(\omega', \omega) = (270^\circ, 300^\circ)$ corresponding to the g^-g^- region.

Fig. 3 presents the $(\omega'-\omega)$ conformational map of the same molecule but with the phosphate geometry favoring the g^+g^+ region. The global minimum is now situated in the g^+g^+ region at $(\omega', \omega) = (60^\circ, 60^\circ)$. It is thus seen that the geometries of the phosphate group which favor respectively the g^-g^- or g^+g^+ regions in the molecule of dimethyl phosphate [12], favor the same regions when the two terminal methyl groups are replaced by sugars in their C(3')-endo puckers. This result confirms the rule established in one of our preceding papers [12]. The available X-ray crystal structure data of di-, tri- and polynucleotides corresponding to the (3'-5')-linked C(3')-endo riboses are plotted in

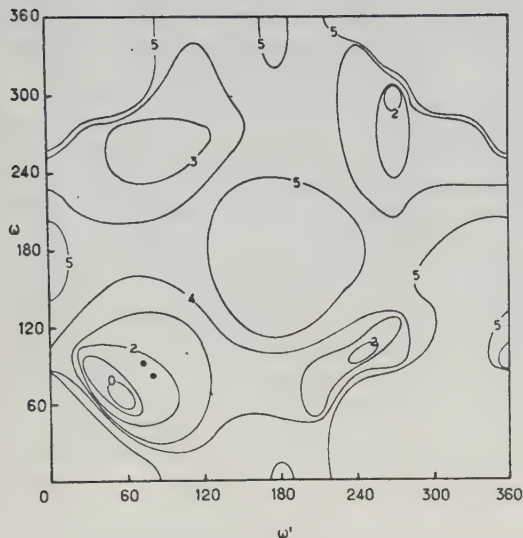


Fig. 3. (ω' - ω) conformational energy map of (3'-5')-linked (C(3')-endo, C(3')-endo) diribose monophosphate with the phosphate group geometry taken from UpA2 [28] which favors the left-handed folded conformation. Isoenergy curves (kcal/mole) with respect to the global minimum taken as energy zero. (●) X-ray crystal structure data.

the respective map following whether they are right- or left-handed folded. In Fig. 2 all the points cluster around the global minimum with the exception of one which corresponds to $U_3 \cdot p_5 \cdot A$ (Molecule 1) [28]. It has been shown in our preceding paper [12] that, in fact, this molecule does not possess a phosphate geometry favoring the g^-g^- and g^+g^+ regions. In Fig. 3 the two available experimental points are near the global minimum. The (ω' - ω) conformational energy map obtained for (C(3')-endo, C(3')-endo) diribose monophosphate in one of our previous articles (ref. 11, Fig. 3) indicates that the g^+g^+ region is of high energy. This previous result corresponded, however, to a diribose monophosphate in which the C(5')-OH group was replaced by a methyl group and the Φ' torsion angle was considered to have the value of about 240° which is larger than the most frequent experimental value [30] of 200° which is adopted in the present article.

The (ω' - ω) conformational maps obtained for (3'-5')-linked (C(3')-endo, C(2')-endo) ribose dimers with the geometries of the phosphate group favoring the g^-g^- or g^+g^+ regions are almost similar to those of the (C(3')-endo, C(3')-endo) dimers, and are not presented here.

Fig. 4 presents the (ω' - ω) conformational map of (3'-5')-linked (C(2')-endo, C(2')-endo) ribose dimer having the geometry of the phosphate group which favors the g^-g^- region. In spite of the tendency of this geometry to favor the g^-g^- region, this region remains a high energy one. This result suggests that the two sugar units must interact strongly in this case. The analysis of the geometrical positions of the sugar atoms indicates indeed that the 2'-OH group

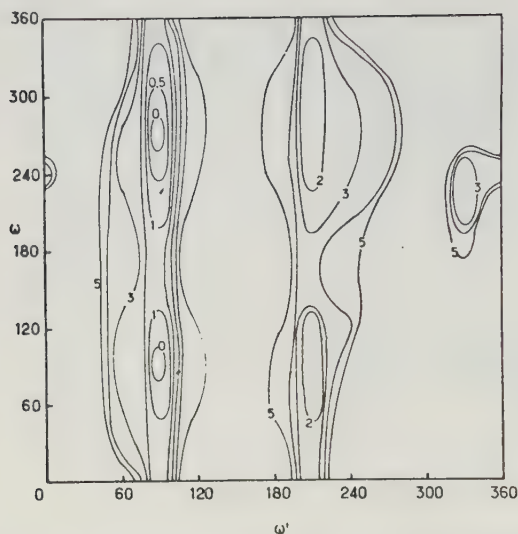


Fig. 4. (ω' - ω) conformational energy map of (3'-5')-linked C(2')-endo, C(2')-endo diribose monophosphate with the phosphate group geometry taken from ApU [31] which favors the right-handed folded conformation. Isoenergy curves (kcal/mole) with respect to the global minimum taken as energy zero.

of the 3'-ribose unit offers close contacts with $O_{1'}$, $C_{4'}$, $C_{5'}$ and $O_{5'}$ atoms of the 5' ribose unit. Two minima appear on Fig. 4, one situated at $(\omega', \omega) = (90^\circ, 270^\circ)$ and the other in the g^+g^+ region $(\omega', \omega) = (90^\circ, 90^\circ)$. This last one becomes 0.5 kcal/mole more stable than the former when the geometry of the phosphate group is changed to the one favoring the g^+g^+ region. (The corresponding map is not presented). As it could be expected, the g^-g^- region remains always in a high energy level, independent of the change of the geometry of the phosphate group.

The (ω' - ω) conformational maps established for (3'-5')-linked (C(2')-endo, C(3')-endo) ribose dimers are similar to the corresponding ones obtained for (C(2')-endo, C(2')-endo) dimers (the maps are not presented). All these results show that the conformational characteristics of ribose dimers are largely dependent on the type of the sugar pucker of the 3'-unit but practically insensitive to the sugar pucker of the 5'-unit.

(3'-5')-Linked deoxyribose dimers. The (ω' - ω) conformational energy maps obtained for these dimers are all similar in their general shape to the maps of Figs 2 and 3 following the geometry adopted for the phosphate group, whether both of the sugars are in the C(3')-endo or the C(2')-endo conformations. (The maps are not presented). The differences occur in the energy levels and surfaces of the g^-g^- and g^+g^+ regions. The most important difference which distinguishes the deoxyribose dimers from ribose dimers is that the (C(2')-endo, C(2')-endo) combination in the case of deoxydimers is no longer restricted in the g^-g^- region and this is due obviously to the absence of the 2'-OH groups, which in the case of ribose dimers with a C(3')-endo sugar pucker in their

3'-unit were preventing these dimers from having the g^-g^- conformation because of close contacts (see preceding section).

The X-ray structure data available on the model molecules of DNA [38] indicate that the conformations of these molecules are close to the g^-g^- conformation.

(2'-5')-Linked ribose dimers. The $(\omega'-\omega)$ conformational maps of (2'-5')-linked (C(3')-endo, C(3')-endo) and (C(3')-endo, C(2')-endo) ribose dimers are similar to the map of Fig. 3. (The maps are not presented). The g^+g^+ region is favored independently of the geometry of the phosphate group and this result suggests a possible interaction between the sugars due to the (2'-5') linkage in the g^+g^+ or g^-g^- region. The conformational maps obtained in the cases of (C(2')-endo, C(2')-endo) and (C(2')-endo, C(3')-endo) dimers are similar to those of Figs 2 and 3 with the only difference that the g^-g^- and g^+g^+ regions in (2'-5')-linked dimers are more extended and the maps more flat. These last results indicate that (2'-5')-linked ribose dimers are more flexible than (3'-5')-linked ribose dimers, and this is probably so because the constituents of the sugar units are farther apart than in the corresponding (3'-5')-linked ribose dimers.

Probability calculations

1. *The effect of the sugar pucker and linkage.* We have indicated in Table I the probabilities of occurrence of the g^-g^- and g^+g^+ regions for all the $(\omega'-\omega)$ conformational energy maps obtained.

In the (3'-5')-linked ribose dimers, the combinations of the sugar puckers which are the most favorable for their occurrence in the g^-g^- region are (C(3')-endo, C(3')-endo) and (C(3')-endo, C(2')-endo) provided the geometry of the phosphate group is the one which favors this region. On the contrary, the (C(2')-endo, C(2')-endo) and (C(2')-endo, C(3')-endo) combinations are unlikely to lead to a g^-g^- conformation, its probability of occurrence being then less than 1% in spite of the same geometry for the phosphate. The first part of these predictions is confirmed by experiment, the available X-ray crystal data on dinucleoside monophosphates, which all correspond to the (C(3')-endo, C(3')-endo) combination (with one exception which is (C(3')-endo, C(2')-endo)) indicating that all of them exist in the g^-g^- conformation. No information seems available on dinucleoside monophosphates with the two other combinations of the sugar puckers.

All the combinations of the sugar puckers correspond to a non-negligible probability of the g^+g^+ region. When the geometry adopted for the phosphate is the one which favors the g^+g^+ conformation, all combinations of the sugar puckers yield such a conformation, the most favorable combination being (C(3')-endo, C(3')-endo).

In the (3'-5')-linked deoxyribose dimers, the two combinations of the sugar puckers which have been considered, (C(3')-endo, C(3')-endo) and (C(2')-endo, C(2')-endo), correspond to an appreciable probability of the g^-g^- region, provided that the geometry of the phosphate group is the one which favors this region. In these dimers the (C(2')-endo, C(2')-endo) combination of the sugar puckers with a geometry of the phosphate group which comes from (ApU) corresponds to a substantial probability of occurrence of the g^-g^- region

TABLE I

The probabilities of occurrence of the g^-g^- and g^+g^+ regions in the different disugar monophosphates. (The geometries of the phosphate group in (ApU) [31] and (UpA2) [28] favor respectively the g^-g^- and g^+g^+ conformations in dimethyl phosphate.)

Dimers	Linkage	Phosphate group geometry	Sugar puckers	Probabilities of occurrence (%)	
				g^-g^- region	g^+g^+ region
Diribose monophosphate	(3'-5')	from (ApU) [31]	(C(3')-endo, C(3')-endo)	62.3	13.8
			(C(3')-endo, C(2')-endo)	74.6	3.4
			(C(2')-endo, C(2')-endo)	0.4	29.6
			(C(2')-endo, C(3')-endo)	0.4	28.5
		from (UpA2) [28]	(C(3')-endo, C(3')-endo)	2.9	83.2
			(C(3')-endo, C(2')-endo)	13.4	50.6
			(C(2')-endo, C(2')-endo)	0.1	55.2
			(C(2')-endo, C(3')-endo)	0.1	53.3
Dideoxyribose monophosphate	(3'-5')	from (ApU)	(C(3')-endo, C(3')-endo)	38.7	27.2
			(C(2')-endo, C(2')-endo)	55.9	5.8
		from (UpA2)	(C(3')-endo, C(3')-endo)	0.8	88.3
			(C(2')-endo, C(2')-endo)	6.3	51.6
Diribose monophosphate	(2'-5')	from (ApU)	(C(3')-endo, C(3')-endo)	18.3	46.6
			(C(3')-endo, C(2')-endo)	23.9	30.5
			(C(2')-endo, C(2')-endo)	35.4	9.5
			(C(2')-endo, C(3')-endo)	35.1	9.1
		from (UpA2)	(C(3')-endo, C(3')-endo)	0.7	86.3
			(C(3')-endo, C(2')-endo)	1.3	76.3
			(C(2')-endo, C(2')-endo)	4.4	49.1
			(C(2')-endo, C(3')-endo)	4.5	50.6

and this result is in contrast with that obtained for the corresponding (3'-5')-linked ribose dimer which has a negligible probability of the same region. When the geometry adopted for the phosphate is the one which favors the g^+g^+ conformation, the two combinations of the sugar puckers in deoxyribose dimers yield such a conformation, the most favorable combination being (C(3')-endo, C(3')-endo).

In the case of the (2'-5')-linked dimers, all the combinations of the sugar puckers favor their occurrence in the g^-g^- and g^+g^+ region when the geometry used for the phosphate group comes from (ApU). In this case dimers with (C(2')-endo, C(2')-endo) and (C(2')-endo, C(3')-endo) combinations of the sugar puckers favor the g^-g^- conformation more than the g^+g^+ conformation. In the case of (2'-5')-linked ribose dimers with the (C(3')-endo, C(3')-endo) and (C(3')-endo, C(2')-endo) combinations of the sugar puckers the g^+g^+ conformation prevails. When the geometry adopted for the phosphate comes from (UpA2) all the combinations of the sugar puckers in the (2'-5')-linked dimers yield the g^+g^+ conformation, the most favorable combinations being (C(3')-endo, C(3')-endo) and (C(3')-endo, C(2')-endo).

Altogether, the greatest probability of occurrence of a g^-g^- conformation is found in the case of a (3'-5')-linked ribose dimer, followed by a (3'-5')-linked deoxyribose dimer and next by a (2'-5')-linked ribose dimer. The greatest

probability of occurrence of the g^+g^+ conformation is on the contrary found in the case of a (3'-5')-linked deoxyribose dimer followed by a (2'-5')-linked ribose dimer and then a (3'-5')-linked ribose dimer.

2. *The effect of the geometry of the phosphate group on the preferred conformations of the diribose monophosphates.* In this section we try to investigate to what an extent a rule established in one of our previous articles [12] remains valid in model molecules of disugar monophosphates following a variation in the linkage and sugar pucker.

We have shown previously [12] that the geometries of the phosphate group of (ApU) and (UpA2) were favoring the right- and left-handed conformations, respectively, in the molecule of dimethyl phosphate.

Following Table I, the g^+g^+ conformations are strongly favored over the g^-g^- ones, in all the dimers considered, when the geometry used for the phosphate group comes from (UpA2). This result is in agreement with the already stated rule [12]. In none of the cases studied do the effects of the sugar puckers and linkages change the preferred left-handed folded conformation predicted by the rule. The situation is different when the geometry of the phosphate group comes from (ApU) which, following the rule, should favor the g^-g^- conformation. In the (3'-5')-linked ribose dimers the rule is valid for the dimers having the C(3')-endo sugar pucker in their 3'-unit. On the contrary, the (3'-5')-linked dimers having a C(2')-endo sugar pucker in their 3'-unit prefer the g^+g^+ region over the g^-g^- region, in exception to the rule. This result points out a substantial effect of the sugar pucker. As far as the deoxyribose dimers are concerned the rule is valid for both cases whether the geometry of the phosphate group comes from (ApU) or (UpA2). In the (2'-5')-linked ribose dimers the rule is valid for dimers which have a C(2')-endo sugar pucker in their 2'-unit, when the geometry used for the phosphate group comes from (ApU). In the two remaining cases of the (2'-5')-linked ribose dimers in which the sugar of the 2'-unit has a C(3')-endo pucker and the geometry used for the phosphate group comes from (ApU), the g^+g^+ region is favored over the g^-g^- region.

Discussion and Conclusions

The principal conclusion which can be drawn from these calculations appears to be that the disugar backbone provides stable conformational arrangements in the right- and left-handed folded conformations, the stability of which depends to a large extent on the geometry of the phosphate group, the nature of the linkage and of the sugar puckers. It has been shown in our preceding article [12] that the g^-g^- and the g^+g^+ regions are already stable regions in dimethyl phosphate and that the occurrence of one or the other of these regions depends on the geometry of the phosphate group; the former is favored when the $O_5, PO(I)$ and $O_3, PO(II)$ valence angles are greater than would have been their symmetrical value and the second is favored when these same valence angles are smaller than their symmetrical value. This rule is valid for the majority of the disugar monophosphates studied in this article for which the occurrence of the g^-g^- and g^+g^+ conformations depends to a large extent on the geometry used for the phosphate group. In a few cases associated with specific combinations of the linkage and the sugar puckers the preferred

conformations predicted by the above rule are changed (see Table I for the details). As far as the effect of linkage is concerned, quite generally the greatest probability of occurrence of the g^-g^- conformation is found for (3'-5')-linked dimers and the greatest probability of occurrence of the g^+g^+ conformation for (3'-5')-linked deoxyriboses and (2'-5')-linked ribose dimers.

It is essential to underline that these results are obtained without the interference of the bases which have not been introduced in these calculations. They express thus an intrinsic tendency of the sugar phosphate backbone towards these conformations.

Olson and Flory [41] in their theoretical calculations on the (3'-5')-linked ribose monophosphate, using partitioned potential energy functions, failed to find the g^-g^- and g^+g^+ regions as the most stable areas, predicting the extended conformation ($\omega' = 180^\circ$, $\omega = 180^\circ$) as the most stable one with a C(3')-endo sugar pucker for both units. These results are not in agreement with experimental data in which the extended conformation is not observed and disagree with the present PCILO calculations which predict the g^-g^- and g^+g^+ conformations as the most stable ones. It may be pointed out that *ab initio* calculations [42] carried out on the model molecule of dimethyl phosphate indicate also that the extended conformation is 7 kcal/mole higher than the g^+g^+ and g^-g^- conformations. PCILO calculations [12] carried out on the same model compound indicate that the extended conformation is at least 3-4 kcal/mole above the folded conformations.

It is striking to observe that the principal conclusions agree very satisfactorily with the experimental results obtained with base-carrying dinucleoside phosphates. In particular a large amount of experimental studies in solution, using a large variety of methods (e.g. proton magnetic resonance, circular dichroism, ultra violet absorbance) [14,15,22] and a variety of dinucleoside phosphates confirms their preference for the right- and left-handed folded conformations and confirm also the increased probability of occurrence of the (2'-5')-linked dimers in the left-handed folded conformation as compared with the (3'-5')-linked analogs.

This situation leaves open the question of the exact role of the bases in the selectivity of these helical type conformations. As it is known, the experimental evaluation of the relative amount of base stacking in different types of dinucleoside phosphates is a subject of controversy. Circular dichroism studies tend to indicate the following order of stacking [15,23,24]; (3'-5')-linked dimers > (2'-5')-linked dimers, while ultraviolet absorbance and proton magnetic resonance methods seem to favor the reverse order [15]; (2'-5')-linked dimers > (3'-5')-linked dimers. Kondo et al. [15], in a critical attempt to unify the results, arrived at the conclusion that (2'-5')-linked dimers must have a greater overlapping of bases than the (3'-5')-linked dimers. The same controversy exists about deoxyribose dimers, for which circular dichroism studies predict a less stacked conformation than for ribose dimers [16,23] while ultraviolet absorbance and proton magnetic resonance methods lead to the reverse conclusions [16]. Kondo et al. [16], in their unifying attempt, propose a larger base-base overlapping in deoxyribose dimers than in ribose dimers.

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